Application of ADAFs for TCE Risk Assessment

Examples from the October 2009 External Review Draft Toxicological Review of Trichloroethylene.

5.2.3.3.1. Example application of age-dependent adjustment factors (ADAFs) for inhalation exposures. For inhalation exposures, assuming ppm equivalence across age groups, i.e., equivalent risk from equivalent exposure levels, independent of body size, the calculation is fairly straightforward. The ADAF-adjusted lifetime cancer unit risk estimate for kidney cancer alone is calculated as follows:

Kidney (ONLY) Cancer Risk - Inhalation Exposure to TCE: 1 µg/m3, ages 0–70:					
Age Group	**ADAF**	**IUR** (ug/m3)-1	**[TCE]** (ug/m3)	**Duration Adjust**	**Risk**
0 – 2 y.o.	10	1x10-6	1.0	2 yr/70 yr	2.9x10-7
2 – 16 y.o.	3	1x10-6	1.0	14 yr/70 yr	6.0x10-7
16 – 70 y.o.	1	1x10-6	1.0	54 yr/70 yr	7.7x10-7
				Total:	**1.7x10-6**
Note that the partial risk for each age group is the product of the values in columns 2−5 [e.g., 10 × (1.0 × 10-6) × 1 × 2/70 = 2.9 × 10-7], and the total risk is the sum of the partial risks. This 70-year risk estimate for a constant exposure of 1 µg/m3 is **equivalent to a lifetime unit risk of 1.7 × 10-6 per µg/m3, adjusted for early-life susceptibility**, assuming a 70-year lifetime and constant exposure across age groups.					

In other words, the lifetime unit risk estimate for kidney cancer alone, adjusted for potential increased early-life susceptibility is 1.7-times the unadjusted unit risk estimate. Adding a 3-fold factor to the unadjusted unit risk estimate to account for potential risk at multiple sites ("1-fold" of the factor of four for multiple sites is already included in the 1.7-times adjustment for early-life susceptibility) yields a total adjustment factor of 4.7. Applying a factor of 4.7 to the unit risk estimate based on kidney cancer alone results in a total cancer unit risk estimate of 2.6 × 10-2 per ppm (4.8 × 10-6 per µg/m3) of constant lifetime TCE exposure, adjusted for potential early-life susceptibility.

Note that the above calculation for adjusting the ADAF-adjusted lifetime unit risk estimate for multiple sites is equivalent to adjusting each ADAF by adding a factor of three and applying those factors as age-specific adjustment factors for both early-life susceptibility and multiple sites to the unadjusted kidney cancer unit risk estimate (i.e., 13, 6, and 4 for <2 years, 2 to <16 years, and ≥16 years, respectively). The total cancer risk estimate of 4.7 × 10-6 per µg/m3, adjusted for potential increased early-life susceptibility, derived below for a constant exposure of 1 µg/m3 differs from the unit risk estimate of 4.8 × 10-6 per µg/m3 presented above only because of round-off error.

Total Cancer Risk - Inhalation Exposure to TCE: 1 µg/m3, ages 0–70:					
Age Group	**ADAF**	**IUR** (ug/m3)-1	**[TCE]** (ug/m3)	**Duration Adjust**	**Risk**
0 – 2 y.o.	13	1x10-6	1.0	2 yr/70 yr	3.7x10-7
2 – 16 y.o.	6	1x10-6	1.0	14 yr/70 yr	1.2x10-6
16 – 70 y.o.	4	1x10-6	1.0	54 yr/70 yr	3.1x10-6
				Total:	**4.7x10-6**
Note that the partial risk for each age group is the product of the values in columns 2−5 [e.g., 13 × (1.0 × 10-6) × 1 × 2/70 = 3.7 × 10-7], and the total risk is the sum of the partial risks. This 70-year risk estimate for a constant exposure of 1 µg/m3 is **equivalent to a lifetime unit risk of 4.7 × 10-6 per µg/m3, adjusted for early-life susceptibility**, assuming a 70-year lifetime and constant exposure across age groups.					

This total cancer unit risk estimate of 2.6 × 10-2 per ppm (4.8 × 10-6 per µg/m3), adjusted for potential increased early-life susceptibility, is only minimally (17.5%) increased over the unadjusted total cancer unit risk estimate because the kidney cancer risk estimate that gets adjusted for early-life susceptibility is only part of the total cancer risk estimate. Thus, foregoing the ADAF adjustment in the case of full lifetime calculations will not seriously impact the resulting risk estimate. *For less-than-lifetime exposure calculations, the impact of applying the ADAFs will increase as the proportion of time at older ages decreases.* The maximum impact will be when exposure is for only the first 2 years of life, in which case the partial lifetime total cancer risk estimate for exposure to 1 µg/m3 adjusted for potential increased early-life susceptibility is 13 × (1 µg/m3) × (1.0 × 10−6 per µg/m3) × (2/70), or 3.7 × 10-7, which is over 3 times greater than the unadjusted partial lifetime total cancer risk estimate for exposure to 1 µg/m3 of 4 × (1 µg/m3) × (1.0 × 10−6 per µg/m3) × (2/70), or 1.1 × 10-7.

5.2.3.3.2. Example application of age-dpendent adjustment factors (ADAFs) for oral exposures.
For oral exposures, the calculation of risk estimates adjusted for early-life susceptibility is complicated by the fact that for a constant concentration of TCE in drinking water, doses will vary by age because of different age-specific drinking water consumption rates. The calculations below illustrate the general approach to applying ADAFs, using lifetime exposure to 1 µg/L of TCE in drinking water as an example.

Age-specific DW ingestion rates were taken from the Child-Specific Exposure Factors Handbook; 90th percentile values were taken from Table 3-19. Data for "consumers only" were used because formula-fed infants (vs. breast-fed infants), children, and young adolescents are the population of concern. For the 16+ age group, the standard default rate for adults was used (i.e., 2 L/day ÷ 70 kg, or 0.029 L/kg/day) (U.S. EPA, 1997, page 3-1), which is identical to the 90th percentile for the 18 to <21 age group. The different age-specific rates were collapsed into the same age groupings as the ADAFs using a time-weighted averaging (Table 5-41).

Table 5-41. Estimates of age-specific water ingestion rates (90th percentile)

Age	**DW Ingestion** (l/kg-d)
Birth – 1 month	0.238
1 – 3 months	0.228
3 – 6 months	0.148
6 – 12 months	0.112
1 -2 years	0.056
0 – 2 y.o.	**0.103**
2 -3 years	0.052
3 – 6 years	0.049
6 – 11 years	0.035
11 – 16 years	0.026
2 – 16 y.o.	**0.036**
16 – 70 y.o.	**0.029**

For simplicity, the adjustments for potential cancer risk at multiple sites and for potential increased early-life susceptibility are made simultaneously using age-specific combined adjustment factors, as was done in the second (equivalent) lifetime risk calculation for inhalation exposures in Section 5.2.3.3.1.

In the case of oral cancer risk, however, the ratio for total risk relative to kidney cancer risk was about five (see Section 5.2.2.3); thus, a factor of four is added to each of the ADAFs to account for risk of tumor types other than kidney cancer. The calculations for the combined adjustment are shown in Table 5-42.

Because the TCE intake is not constant across age groups, one does not calculate a lifetime unit risk estimate in terms of risk per mg/kg/d adjusted for potential increased early-life susceptibility. One could calculate a unit risk estimate for TCE in drinking water in terms of µg/L from the result in Table 5-42, but this is not something that is commonly reported, and it is dependent on the water ingestion rates used.

Total Cancer Risk – DW Ingestion Exposure to TCE: 1 µg/l, ages 0–70:						
Age Group	**Combined AF**	**Unit Risk** (mg/kg-d)-1	**[TCE]** (mg/l)	**Ingest Rate** (l/kg-d)	**Duration Adjust**	**Risk**
0 – 2 y.o.	14	9.3x10-3	0.001	0.103	2 yr/70 yr	3.8x10-7
2 – 16 y.o.	7	9.3x10-3	0.001	0.036	14 yr/70 yr	4.7x10-7
16 – 70 y.o.	7	9.3x10-3	0.001	0.029	54 yr/70 yr	1.0x10-6
					Total:	**1.9x10-6**
Unit risk estimate for kidney cancer based on primary dose metric, from Table 5-40.						

As with the adjusted inhalation risk estimate in Section 5.2.3.3.1, the lifetime total cancer risk estimate of 1.9×10^{-6} calculated for lifetime exposure to 1 µg/L of TCE in drinking water adjusted for early-life susceptibility is only minimally (25%) increased over the unadjusted total cancer unit risk estimate. (This calculation is not shown, but if one uses just the factor of five for potential cancer risk at multiple sites for each of the age groups in Table 5-42, the resulting total lifetime risk estimate is 1.5×10^{-6}.) Unlike with inhalation exposure under the assumption of ppm equivalence, the oral intake rates are higher in the potentially more susceptible younger age groups. This would tend to yield a larger relative impact of adjusting for early-life susceptibility for oral risk estimates compared to inhalation risk estimates. In the case of TCE, however, this impact is partially offset by the lesser proportion of the total oral cancer risk that is accounted for by the kidney cancer risk, which is the component of total risk that is being adjusted for potential increased early-life susceptibility, based on the primary dose metrics (1/5 vs. 1/4 for inhalation). Thus, as with lifetime inhalation risk, foregoing the ADAF adjustment in the case of full lifetime calculations will not seriously impact the resulting risk estimate. For less-than-lifetime exposure calculations, the impact of applying the ADAFs will increase as the proportion of time at older ages decreases. The maximum impact will be when exposure is for only the first 2 years of life, in which case the partial lifetime total cancer risk estimate for exposure to 1 µg/L adjusted for potential increased early-life susceptibility is 3.8×10^{-7} (from Table 5-42), which is almost 3 times greater than the unadjusted partial lifetime total cancer risk estimate for exposure to 1 µg/L of $5 \times (0.001$ mg/L) × (0.103 L/kg/day) × (9.33 × 10−3 per mg/kg/d) × (2/70), or 1.4 × 10-7.